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3-25-92

☒ This application has been examined ☒ Responsive to communication filed on election 12/27/82 change of address ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), Ø days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☒ Notice re Patent Drawing, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO 152
5. ☒ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 1-76 are pending in the application.
   Of the above, claims 67-76 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-66 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☒ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

15. Applicant's election with traverse of Group I, claims 1-62 in Paper No. 9 is acknowledged. The traversal is on the ground(s) that;

A) The method of group II, claims 63-66 is the same as that of group I, this argument was found persuasive and claims 63-66 have been examined in the instant application,

Further, applicants traversal continues,

B) That the assay of group III, claims 67-76, relies on the ability of the ligand to be recognized by the target receptor, which is an inherent property of the CD28 receptor. This is not found persuasive because these claims are directed to an assay. An assay clearly differs from a method of regulating in that it is used as a detection method. The mechanism may be inherent but the process steps differ, thus requiring not only a different search but also different considerations regarding patentability.

The requirement is deemed proper and is therefore made FINAL. Claims 1-66 were examined

16. Applicant is encouraged to file an Information Disclosure Statement including (1) a form PTO-1449, "Information Disclosure Citation" listing patents, publications and other information material to the instant application, (2) a concise explanation of the relevance of each listed item and (3) a copy of each listed item. See 37 C.F.R. 1.97 through 1.99 and MPEP 609 and 2001.06 through 2004 for further guidance.

17. 35 U.S.C. § 101 reads as follows:
"Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

18. Claims 1-66 are rejected under 35 U.S.C. § 101 because the specification fails to adequately teach how to use the claimed B7 antigen protein/fusion protein, CD28 protein/fusion protein and monoclonal antibodies, in compositions to achieve an in-vivo therapeutic, effective as a method for regulating T cell responses. Particularly in regulating T-cell responses, treating cancer, lymphoma, leukemia and graft versus host disease. Applicants claims are supported only by in-vitro data. Applicant has made no showing that the data correlate with utility for in-vivo therapy in humans. Further, in-vitro data such as that reported in the specification and animal model studies frequently do not correlate with clinical utility in in- vivo trails in

patients. Based on the evidence of record, the alleged utility of the claimed compositions for the regulation of T cell responses would not be believable on its face to the person of skill in the art in view of the contemporary knowledge in the art. Applicant has not provided any showing of therapeutic utility of the subject compositions which would lead one of skill in the art to believe that the antibodies are broadly applicable for the regulation of T cell responses in humans. See MPEP 608.01(p).

19. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

20. The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure.

A) Applicants have not disclosed to one f ordinary skill in the art how to use the protein as a pharmaceutical or therapeutic agent. There is an insufficient written description of the invention with respect to the in-vivo operability of the protein to enable one of ordinary skill in the art to use applicant's invention, for the reasons discussed in detail in the previous rejection made under 35 U.S.C. § 101. ~~Furthermore,~~ applicant has provided no teaching or guidance indicating what dosages are required and what way(s) the protein can be administered (see Ex parte Powers, 220 U.S.P.Q. 924 (Bd. Pat. App. & Int. 1982)) or otherwise used in a practical manner. It would, therefore, require undue experimentation of one of ordinary skill in the art to determine how to use the claimed protein for the reasons previously discussed. See Ex parte Forman, 230 U.S.P.Q. 546 (Bd. Pat. App. & Int. 1986).

~~B)~~ Applicants referral to the deposits on page 13, lines 7-11, B7Ig fusion and lines 19-22, CD28Ig fusion respectively are insufficient assurance that all required deposits have been made and all the conditions of MPEP 608.01(p)(c) met. Further the deposits of the monoclonal antibodies which recognize these proteins is required. Therefore the following are required;

(1) A statement confirming the deposit of the fusion protein transformants and hybridoma cell lines which produce the antibodies which recognize the fusion proteins,
(2) A copy of the contract with the depository,
(3) Amendment of the specification to recite the complete name and street address of the depository,
(4) An averment from the attorney having authority and control over the conditions of deposit or signed by assignee, or all applicants, affirming compliance with the regulations of MPEP 608.01(p).

Applicants attention is directed to MPEP 608.01(p)(c), and deposit rules 1106 OG 37-54, for further information concerning deposit practice.

21. Claims 1-66 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

22. Claims 1-66 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited in-vitro regulation of T cell responses. See M.P.E.P. §§ 706.03(n) and 706.03(z).

23. Claims 15, 16 and 21 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 15 and 16 are indefinite in the recitation of the term "anti-CD". It is unclear what the term "anti-CD" refers to. "anti-CD" is a non-descriptive term. It may represent a particular CD# antigen however the exact antigen is unknown. If "anti-CD" refers to a particular CD# antibody the exact antigens must be incorporated into the claim language. For example anti-CD3 antibody. The claim is required to be amended to definitively identify the subject matter being claimed. Applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter.

B) Claim 21 is indefinite in the use of the period after antigen, see second line of the claim. It is unclear whether the claim was intended to end with this period or include the third line. The claim is required to be amendment to clarify this issue.

24. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under

this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

and;

> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

25. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

26. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

27. Claims 1, 15, 16, 35-40, ~~43-45~~, 50-52, 55, 56, ~~58~~, 59, 60, 63, and 66 are rejected under 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious over Damle, et. al. Damle, et. al., teach that the CD28 molecule is expressed on the surface of a majority of human T cells and has been implicated to play an active role in the regulation of T cell growth, see abstract. They use an anti-CD28 singly and in combination with anti-CD3 antibodies to show its effect on T-cell stimulation and cytokine induction, see abstract and page 1753, column 2, lines 33-46. This antibody would therefore inherently inhibit, claim 55, or stimulate, claim 56, functional T cell responses, including the production of cytokines, which include interleukins, interferons, transforming growth factors, TNF and CSF. Damle, et. al., incorporate by reference the teachings of Martin, et. al., see reference 29. Martin, et. al., teach the monoclonal antibody 9.3. Therefore the monoclonal antibody will inherently recognize the CD28 receptor as a membrane protein or as a soluble fusion protein. Methods of producing proteolytic antibody fragments were well known in the art at the time the invention was made. It is clear in the art that antibodies to cell adhesion molecules can inhibit T cell activation and therefore are potentially important in treating immune system diseases, including, cancers such as T cell leukemias, and graft versus host disease. The drug cyclosporine was well known as an immunosuppressant prior to the date of the applicants invention.

28. Claims 1-66 are provisionally rejected under 35 U.S.C. § 103 as being obvious over copending application Serial No. 07/547980.

Copending application Serial No. 07/547980 has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the copending application, it would constitute prior art under 35 U.S.C. § 102(e) if patented. This provisional rejection under 35 U.S.C. § 103 is based upon a presumption of future patenting of the conflicting application.

This provisional rejection might be overcome either by a showing under 37 C.F.R. § 1.132 that any unclaimed invention disclosed in the copending application was derived from the inventor of this application and is thus not the invention "by another", or by a showing of a date of invention prior to the effective U.S. filing date of the copending application under 37 C.F.R. § 1.131.

29. Claims 1-66 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1-29 of copending application Serial No. 07/547,980. Although the conflicting claims are not identical, they are not patentably distinct from each other because they each are directed to a method of regulating T cell responses by modulating the interaction between CD28 and the B7 antigen.

This is a provisional obviousness-type double patenting

rejection because the conflicting claims have not in fact been patented.

30. The obviousness-type double patenting rejection is a judicially established doctrine based upon public policy and is primarily intended to prevent prolongation of the patent term by prohibiting claims in a second patent not patentably distinct from claims in a first patent. In re Vogel, 164 USPQ 619 (CCPA 1970). A timely filed terminal disclaimer in compliance with 37 C.F.R. § 1.321(b) would overcome an actual or provisional rejection on this ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R. § 1.78(d).

31. Claims 1, 15, 16, 35-40, 48-49, 50-52, 55, 56, 58, 59, 60, 63, and 66 are rejected under 35 U.S.C. § 103 as being unpatentable over Damle, et. al. Damle, et. al., teach that the CD28 molecule is expressed on the surface of a majority of human T cells and has been implicated to play an active role in the regulation of T cell growth, see abstract. They use an anti-CD28 singly and in combination with anti-CD3 antibodies to show its effect on T-cell stimulation and cytokine induction, see abstract and page 1753, column 2, lines 33-46. Damle, et. al., incorporate by reference the teachings of Martin, et. al., see reference 29. Martin, et. al., teach the monoclonal antibody 9.3. Damle, et. al., do not specifically teach the use of the antibody in a method of regulating T cell responses. However, since the antibody is the same as that of Martin, et. al., and in considering the contemporary knowledge in the art at the time the invention was made it would have been prima facia obvious to a person of ordinary skill in the art to use the CD28 antibody as a method of regulating T cell responses. This antibody would inherently inhibit, claim 55, or stimulate, claim 56, functional T cell responses, including the production of cytokines, which include interleukins, interferone, transforming growth factors, TNF and CSF. The monoclonal antibody will inherently recognize the CD28 receptor as a membrane protein or as a soluble fusion protein. Methods of producing proteolytic antibody fragments were well known in the art at the time the invention was made. It is clear in the art that antibodies to cell adhesion molecules can inhibit T cell activation and therefore are potentially important in treating immune system diseases, including, cancers such as T cell leukemias, and graft versus host disease. The drug cyclosporine was well known as an immunosuppressant prior to the date of the applicants invention.

32. Art made of record but not relied upon are as follows.

A) Freeman, et. al., J. Immunology 139:3260-3267, 1987. This reference teaches that B7 is expressed on a subpopulation of B lymphocytes and a B7 monoclonal antibody, see page 3262, column

1, lines 27-31. This reference however does not teach the CD28 molecule as a receptor for the B7 antigen. Further the reference does not suggest the use of the antibody as a method of regulating T cell responses.

B) Freeman, et. al., J. Immunology 143:2714-2722, 1989. This reference teaches the molecular cloning and sequencing of the B7 antigen. This reference however does not teach the CD28 molecule as a receptor for the B7 antigen or the use of the B7 molecule in a method of regulating T cell responses.

C) Martin, et. al., J. Immunology 136:3282-3287, 1986. This reference teaches the CD28 antibody 9.3, see abstract.

33. No claims are allowed.

34. Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4227.

35. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Donald E. Adams whose telephone number is (703) 308-3997. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 180 receptionist whose telephone number is (703) 308-0196.

March 18, 1992

Donald E. Adams, Ph.D. DEA

JOHN J. DOLL
SUPERVISORY PATENT EXAMINER
GROUP 180